111-1060 08

Solution

Patent
Attorney's Docket No. 010095-003g

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of)
)
William R. Pilgrim, et al)
)
U.S. Patent No.: 5,015,758) Attn: Box Patent Extension
)
Issued: May 14, 1991)
)
For: PROCESS FOR THE PREPARATION)
OF 1-ADAMANTANE DERIVATIVES)
)

APPLICATION FOR EXTENSION OF PATENT TERM

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This application is submitted by including an original, a certified copy and three working copies.

Under the provisions of 35 U.S.C. §156 and in accordance with 37 C.F.R. §1.710 *et. seq.*, the owner of record of U.S. Patent No. 5,015,758 ("the '758 Patent"), requests that the term of the '758 Patent be extended 257 days to expire on May 31, 2010. The '758 Patent issued May 14, 1991, and would in view of GATT, and in the absence of an extended term, expire on September 6, 2009. The named inventors are William R. Pilgrim and Joel Lagiere. The patent is assigned of record to Centre International de Recherches Dermatologiques ("CIRD"), Valbonne, France. The patent is licensed to Galderma

Laboratories, Inc., who was the marketing applicant for the NDA for DIFFERIN Solution, 0.1%. As background, Centre International de Recherches Dermatologiques (CIRD) and Galderma Laboratories, Inc. are both organizations existing under the joint ownership of Nestlé S.A. and L'Oréal.

The items required by 37 C.F.R. §1.740(a) follow in §§ I-XVII.

I. APPROVED PRODUCT

The approved product, having the tradename "DIFFERIN Solution, 0.1%", is a solution containing adapalene. Each milliliter (ml) of DIFFERIN Solution contains adapalene 0.1% (1 mg), in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v). Specifically, DIFFERIN contains, per g, the following ingredients:

Ingredient	per g	percent (w/w%)
adapalene	1 mg	0.10%
polyethylene glycol 400. NF	0.699 g	69.9%
SD alcohol 40-B, anhydrous	QS to 1 g	QS to 100.0%

The finished dosage form of DIFFERIN has a specific gravity of 1.003-1.009. Since DIFFERIN Solution is in the form of a liquid, the concentrations of adapalene and alcohol will be expressed in the form of weight-to-volume measures for labeling purposes.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. The molecular formula is $C_{28}H_{28}O_3$ and the molecular weight is 412.52.

Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water.

The approved use of DIFFERIN Solution is for the topical treatment of acne vulgaris. Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris.

The approved product is marketed in both a 30 ml and a 60 ml glass bottle with applicator. The applicator is designed so that the solution may be applied directly to the involved skin. The solution may be stored at controlled room temperature of 20°-25°C (68°-77°F).

II. APPLICABLE FEDERAL STATUTE

The approved product, DIFFERIN Solution, was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("the Act").

III. PRODUCT APPROVAL DATE

The approved product, DIFFERIN Solution, received permission for commercial marketing or use under Section 505 of the Act on May 31, 1996.

IV. IDENTIFICATION OF DRUG PRODUCT INGREDIENTS

In accordance with 37 C.F.R. §1.740(a)(4), the active ingredient of DIFFERIN Solution is adapalene, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene has not been previously approved for commercial marketing or use under the Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

V. APPLICATION FILING DEADLINE

The present application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.758(f). The last day on which the application can be submitted is July 29, 1996.

VI. PATENT FOR WHICH EXTENSION IS SOUGHT

The patent for which an extension is being sought is U.S. Patent No. 5,015,758, which issued on May 14, 1991, in the names of William R. Pilgrim and Joel Lagiere. The patent is assigned of record to Centre International de Recherches Dermatologiques (CIRD), Valbonne, France. Since this patent issued before June 8, 1995, the effective date of the Uruguay Round Agreements Act it is entitled to a patent term of the longer of twenty (20) years from the application filing date or seventeen (17) years from the

patent issue date. For the '758 Patent, a patent term of twenty (20) years from the filing date of September 6, 1989, is longer. The patent would thus expire on September 6, 2009.

VII. COPY OF PATENT

A copy of U.S. Patent No. 5,015,758 is enclosed herewith as Appendix A, including the entire specification and claims.

VIII. COPY OF CERTIFICATE OF CORRECTION, DISCLAIMERS, MAINTENANCE FEE PAYMENT RECEIPTS OR REEXAMINATION CERTIFICATES

There is no certificate of correction, disclaimer or reexamination certificate for this patent. Copies of maintenance fee payment receipts are enclosed in Appendix B.

IX. SHOWING THAT PATENT CLAIMS APPROVED PRODUCT

U.S. Patent No. 5,015,758 claims a process for preparing the active ingredient of the approved DIFFERIN product.

The following patent claims read directly on the approved product:

Claim 1 reads on the approved product. Claim 1 recites as follows:

> 1. A process for the preparation of 1-adamantane derivatives characterized by the fact that a 1-acyloxyadamantane, in which the acyl group contains 1 to 4 carbon atoms, is reacted with a receptor compound in a linear aliphatic or cycloaliphatic type solvent in the presence of concentrated sulfuric acid and at ambient temperature.

The chemical name for adapalene, having the chemical formula as set forth in Appendix C, is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. DIFFERIN Gel thus contains a 1-adamantane derivative. Since adapalene may be prepared according to the method of claim 1, claim 1 reads on the approved product.

Claim 2 also reads on the approved product. Claim 2 recites the process of claim 1, "wherein the 1-acyloxyadamantane is 1-formyloxyadamantane, 1-acetoxyadamantane, or 1-propionyloxyadamantane." For making adapalene according to the claimed method, 1-acetoxyadamantane is employed. Claims 3 and 4 also read on the approved product. Claim 3 recites that the linear aliphatic solvent is hexane, heptane, or octane, while claim 4 recites that the solvent is heptane. Claim 5 also reads on the approved product. Claim 5 recites that process of claim 1, "wherein the cycloaliphatic solvent is cyclopentane, cyclohexane, or cyclooctane." For making adapalene, both linear aliphatic solvents, such as hexane, heptane, and octanecyclohexane, or cycloaliphatic solvents, such as cyclopentane, cyclohexane, and cyclooctane, may be employed.

Claims 6 and 7 also read on the approved product. Claim 6 recites a process, wherein the solvent is used "in a proportion of between 5 and 100 times the quantity of the 1-acyloxyadamantane, while claim 7 recites that the "concentrated sulfuric acid is used in a proportion of between 0.1:1 and 0.5:1 in relation to the quantity of 1-acyloxyadamantane."

To make adapalene, the solvent and concentrated sulfuric acid may be used in these proportions.

Claim 8 recites that the "receptor compound is an aromatic compound of the group consisting of anisole, phenol, toluene, naphthalene, thiophene, or furan and their substituted derivatives." Claim 9 recites that the receptor is 4-bromoanisole, 4-bromophenol, 4-methoxybenzoic acid, 4-methoxybenzoate, methyl 2-fluoro-4-methoxybenzoate, allyl-2-fluoro-4-hydroxybenzoate, methyl 6-(4-hydroxyphenyl)-2-naphthoate, methyl 6 -(4-methoxyphenyl)-2-naphthoate or 6-hydroxy-2-bromonaphthalene. According to claim 10, the receptor is 4-methoxybenzene thiol and according to claim 11, the receptor compound is acetonitrile. Since the claimed receptors may be used to make adapalene in accordance with the claimed process, claims 8-11 all read on the approved product.

X. INFORMATION PURSUANT TO 35 U.S.C. §156(g)

The information required by 37 C.F.R. §1.740(a)(10)(v) is set forth below.

An Investigational New Drug (IND) application was filed by Dermatological Products of Texas, Inc. (formerly known as Dermatological Products of Texas, Inc., which company Galderma contracts with for the production and control of drug products under investigational development), for 6-[3-(1-adamantyl)-4-methoxyphenyl-2-naphthoic acid on August 18, 1988 and was received by the FDA on August 19, 1988. The IND became effective on September 18, 1988, thirty (30) days after the date of receipt of the IND. The IND number assigned to 6-[3-(1-adamantyl)-4-methoxyphenyl-2-naphthoic acid was IND 31,997.

A New Drug Application (NDA) was filed by Galderma Laboratories, Inc. (previously known as Owen/Galderma Laboratories, Inc.), on March 19, 1993. The NDA number assigned to the application for DIFFERIN Solution was NDA 20-338. The NDA was approved on May 31, 1996.

Further, the above identified patent is eligible for an extension of patent term, since the following requirements of §156(g) are met:

(1) the above identified patent has not expired prior to the filing of this application for extension of patent term;

(2) the term of the patent has never been extended;

(3) the application for extension of patent term is being submitted by the patent attorney or agent for the owner of record of the above identified U.S. Patent No. 5,015,758 for which a patent term extension is sought, authorized to practice before the U.S. Patent and Trademark Office, who has general authority from said owner to act on behalf of said owner in patent matters including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. §1.740;

(4) the product has been subject to a regulatory review period before its commercial marketing or use in the United States;

(5) the permission for the commercial marketing or use of the product after such regulatory review period is the first such permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

XI. ACTIVITIES DURING REGULATORY REVIEW PERIOD

Significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the dates applicable to such activities areas follows:

September 19, 1989	Dr. Browder, Mr. Davitt and Dr. Osterberg of FDA met with sponsor representatives to discuss the nonclinical studies planned for submission in support of an NDA.
April 27, 1990	A letter from Dr. Murray Lumpkin in which the agency concurred that the sponsor must provide precautionary labeling clearly stating that there have been positive findings relating to photocarcinogenicity for retinoids and related compounds.
November 7, 1990	A pre-NDA meeting, which included Drs. Lumpkin, Burlington, Evans, Rand, Harkins and Ms. Cook of FDA and sponsor representatives. The focus of the meeting was to review the available clinical data from both U.S. and European studies and to assess the completeness of the clinical evidence of safety and efficacy towards making a determination of fileability of an NDA for the drug product. Based on several comments and concerns expressed by agency participants with regard to the one completed vehicle-controlled study, the sponsor elected to conduct an additional vehicle-controlled study (No. 9104-CD271L-EV), which was initiated in March of 1991, and completed in August of 1991. The submission of the NDA was based on the November 7, 1990 meeting discussions and the completion of the subsequent clinical study.
December 3, 1991	A letter from Galderma reaffirming its commitment to include a statement the PRECAUTIONS section of the labeling, which closely followed the statement suggested in Dr. Lumpkin's April 27, 1990, letter.
October 19, 1992	Correspondence to IND 31,997 addressed the matter of submitting "line listings" for patients enrolled in pivotal clinical studies. T

December 14, 1992 Galderma Laboratories, Inc., referred to herein as "the applicant", submitted the Chemistry, Manufacturing and Controls Data section of the NDA pursuant to the provisions of 21 CFR 314.50(d)(1)(iv).

March 19, 1993 Original application submission of remaining sections following Pre-NDA Submission of Chemistry, Manufacturing and Controls Data on December 14, 1992. The application included the following:

VOLUME 2.1
- ITEM 1. INDEX
- ITEM 2. SUMMARY
- ITEM 4.c. LABELING

VOLUMES 2.2 - 2.42
- ITEM 5. NONCLINICAL PHARMACOLOGY and TOXICOLOGY SECTION

VOLUMES 2.43 - 2.44
- ITEMS 6. HUMAN PHARMACOKINETICS and BIOAVAILABILITY SECTION

VOLUMES 2.45 - 2.61
- ITEM 8. CLINICAL AND STATISTICAL DATA SECTION

VOLUMES 2.62 - 2.66
- ITEM 11. CASE REPORT TABULATIONS

VOLUMES 2.67 - 2.68
- ITEM 12. CASE REPORT FORMS

STATISTICAL APPENDIX VOLUMES I - III

March 22, 1993 Desk copies of Volume 2.1 sent to Ms. Rosemary Cook, CSO, FDA.

April 20, 1993 FDA Review Chemist's request for status of manufacturing facilities "inspection readiness.

April 26, 1993 FDA Review Microbiologist's request for Microbial Limits Test data and-Procedure.

April 29, 1993 Applicant's amendment to application in response to Microbiologist's request. Submitted MLA procedure and test results.

April 30, 1993	FDA's request for administrative items to complete "filing review".
May 6, 1993	Applicant's amendment to application in response to "filing review" items and Chemist's request for manufacturing facilities information.
May 11, 1993	FDA's request for information to aid statistical reviewer in use of SAS Data Sets. May 12th memo of telephone call to FDA reviewer by M. Tuley verifying request.
May 12, 1993	FDA's request for Microbial Limits Test data to demonstrate preparatory testing and validity of method.
May 21, 1993	Applicant's amendment to application to provide information to statistical reviewer in partial response to May 11th request and a technical report on preparatory testing to validate the Microbial Limits Test in response to May 12th request.
June 7, 1993	FDA telephone call. Request for copies of Chemistry, Manufacturing and Controls section sent to S.A. Inspection Post. Expressed objection to DIFFERIN trade name.
June 9, 1993	Applicant's amendment to application providing: 1) SAS programs to Statistical Reviewer; and 2) Notification of transmittal of Item 3 & 4 Volumes and amendments to FDA San Antonio inspectors. Copy of letter to Mr. Martinez included.
June 11, 1993	FDA telephone call from Dr. Elhage. Request for Desk Copy of Vol. 2.1 and information on Clinical Studies 9104-CD271L-EV and CR 88043.
June 16, 1993	FDA facsimile transmission dated June 14 providing: 1) Chemistry review comments; and 2) Objection to DIFFERIN name.
June 22, 1993	a) Submission of information to Dr. El Hage in response to his request of June 11, 1993. b) Submission of documents to NDA File.

June 30, 1993	Submission of documents and information to Mr. Martinez in response to inspection of Dermatological Products of Texas, Inc. ("DPT") manufacturing facilities.
July 1, 1993	Response to facsimile transmission of June 14th, providing 1) Chemistry comments; and 2) Objection to tradename.
July 26, 1993	Environmental Assessment review and request for additional information by FDA.
August 12, 1993	Amendment in response to FDA 483 inspection observations.
August 26, 1993	4-Month Safety Update provided by Applicant.
September 17, 1993	Response to Clinical Review comments on 9104-CD271L-EV from D. Bostwick.
September 17, 1993	Facsimile transmission from D. Bostwick with request for tabulated data on clinical studies 9104-CD271L-EV, C-88-26 and C-88-27.
September 17, 1993	M. Tuley memo to the file. FDA Statistician request for assistance with SAS datasets.
September 20, 1993	M. Tuley facsimile transmission to FDA Statistician with Formats for Adapalene Solution Submission.
September 22, 1993	M. Tuley memo to the file. Telephone conversation with Dr. Ralph Harkins on tables for clinical studies 9104-CD271L-EV, C-88-26 and C-88-27.
September 20, 1993	Facsimile transmission from FDA with 10 Chemistry Review comments.
September 24, 1993	Acknowledgment of Chemistry Review comments. Commitment to respond by October 29, 1993.
September 24, 1993	Submission of Clinical Statistical Data Tables for 9104-CD271 L-EV.

September 29, 1993	Submission of Clinical Review Responses (see Tab 2-September 17, 1993) and Diskette of SAS Codes to Statistician Dr. Srinivasan.
October 5, 1993	M. Tuley memo to the file. Telephone conversation of September 30 with D. Bostwick and Dr. Srinivasan. D. Bostwick has recommended approval based on Clinical and Statistical review.
October 27, 1993	Facsimile transmission to R. Cook, FDA, setting forth a commitment for responses to Chemistry Review Comments.
October 29, 1993	Additional Statistical data and diskette as requested by Dr. Srinivasan
October 29, 1993	Volume 1 of 2 - response to FDA chemistry review comments received 9-20-93. Volume 2 of 2 -methods validation package with new and revised procedures.
November 1, 1993	Submission of Field Copy to FDA Dallas District Office.
November 24, 1993	Applicant Submitted: (1) Completed response to FDA Chemistry review comments of September 20, 1993. Analytical methods for THF and Chromatographic Purity in raw material. DPT procedures for alcohol and adapalene in drug product. New lists of Tests, Specifications and Methods for drug substance, finished product and Post-Approval Stability Studies; and (2) Comprehensive resubmission of Methods Validation Package
December 3, 1993	Environmental Assessment resubmission
December 7, 1993	Facsimile transmission to Ms. R. Cook on status of application.
December 8, 1993	Facsimile transmission from Mr. Timper, Chemist, asking two questions regarding: 1) status of EA submission, and 2) availability of impurity samples
December 10, 1993	Response submitted to NDA with facsimile transmission copies to Mr. Timper and Ms. Cook
January 5, 1994	FDA Notification of intent to inspect FINORGA

January 10, 1994	Submission of DPT permit information for EA requested by Dr. Tso.
January 17, 1994	Submission of French and Irish Labeling and notification of pending facilities inspections.
January 31, 1994	Submission of U.S. Clinical Studies Data Tables - Summary without patients on oral antibiotics.
February 23, 1994	Facsimile transmission to R. Cook on status of pending activities: a) FINORGA inspection, b) DPT re-inspection, and c) Pre-clinical review.
February 28, 1994	Safety Update, including status of worldwide marketing applications.
March 2, 1994	Facsimile transmission to R. Cook on submission of pathology (tumor) data. Letter of Authorization for Pharmaco::LSR to submit electronic data to Dr. Lin.
February 24, 1994	FDA extension of user fee date to June 24, 1994.
March 14, 1994	Facsimile transmission to R. Cook on submission of pathology (tumor) data by Pharmaco:: LSR on March 11. Update on FINORGA and DPT inspections.
March 18, 1994	Pre-Clinical - Submission of Pharmaco::LSR support documentation and correspondence to Dr. Lin in re: pathology (tumor) data from carcinogenicity studies.
April 1, 1994	DPT inspection notification February 22 - March 11, 1994 and March 16, 1994 FDA 483. DPT March 29th response submission.
April 4, 1994	April 1994 - Draft labeling submitted by Applicant
April 15, 1994	Telephone call from Ms. R. Cook, informing Applicant that preclinical biostatistical review was completed.
April 26, 1994	Submission of FINORGA response to 483
April 26, 1994	Facsimile transmission to R. Cook on status of application

May 20,1994	Submitted draft labeling, incorporating FDA recommended revisions
May 25,1994	Telephone conversation with R. Cook and Dr. Chambers regarding FDA Draft Labeling
May 27,1994	Facsimile transmission to R. Cook
May 24,1994	FDA Laboratory review comments and recommendations for procedure modifications
June 3, 1994	Submission of revised draft labeling
June 6, 1994	Facsimile transmission to R. Cook on status of application
June 15, 1994	CMC Amendment submitted by Applicant - FINORGA response to FDA letter dated 5/9/94 - Sponsor response to 5/24/94 facsimile transmission of FDA Testing Laboratory comments. (Includes new and revised DFT procedures and Drug Product assay validation.)
June 17,1994	Facsimile transmission to Ms. Rosemary Cook with status of submission amendments
September 2, 1994	Methods Validation Package for Drug Product. Copy submitted to Mr. Jim Hanus FDA Testing laboratory DDO.
November 10, 1994	Facsimile transmission to Rosemary Cook requesting status of application. Amendment with FINORGA responses to September 29-30th Form 483 inspection and CIRD technical report on identification of IM2 impurity.
December 15, 1994	Facsimile transmission to Rosemary Cook requesting status of application.
January 4, 1995	Facsimile transmission to Rosemary Cook requesting status of application.

January 12, 1995	Facsimile transmission to Rosemary Cook with amendment summary for status determinations
February 21, 1995	Amendment with update of Foreign approvals and Canadian Product Monograph.
March 21, 1995	Letter to Rosemary Cook regarding reinspection of FINORGA.
May 1, 1995	CMC Amendment to correct all outstanding deficiencies. Request for change in frosted bottle to nonfrosted and FINORGA Process validation report.
May 10, 1995	Facsimile transmission from J. Timper advising review of FINORGA DMF update.
July 6, 1995	Patent Information submission per URAA
March 29, 1996	FDA Nomenclature Committee review of DIFFERIN Tradename.
May 29, 1996	Facsimile transmission to FDA with revised draft package insert labeling.
May 30, 1996	Amendment with final draft labeling.
May 31, 1996	FDA Approval Letter.

XII. ELIGIBILITY OF PATENT FOR EXTENSION

In the opinion of Applicant, the above identified patent is eligible for an extension of the term for 257 days, and to thus expire on May 31, 2010. The length of the claimed extension of 257 days was determined by Applicant, pursuant to 37 C.F.R. §1.775, to be fourteen years from the date of the FDA final approval, as described below:

A. Length of the Regulatory Review Period (Rule 775(c))

1. Period Pursuant to Paragraph (c)(1)

The period defined at 37 C.F.R. §1.775(c)(1) began on September 18, 1988 (the date the IND became effective) and ended on March 19, 1993 (the date the NDA was filed). The (c)(1) period is thus 1643 days.

2. Period Pursuant to Paragraph (c)(2)

The period defined at 37 C.F.R. §1.775(c)(2) began March 19, 1993 (the date of submission of the NDA submitted pursuant to Section 505(b) of the Act) and ended May 31, 1996 (the commercial marketing and use approval date). The (c)(2) period is thus 1169 days.

The total (c)(1) and (c)(2) time period is thus 2812 days.

B. Term of the Patent as Extended (Rule 775(d))

The term of the patent as extended was then calculated to expire on February 18, 2015, pursuant to 37 C.F.R. §1.775(d).

1. (d)(1) Period (Days Subtracted from Regulatory Review Period)

The regulatory review period upon which the period of extension is calculated by subtracting from the regulatory review period as determined in (c)(1) and (c)(2) of this section the following:

(I) The number of days in the periods of paragraphs (c)(1) and (c)(2) above which were on or before January 5, 1988, the issue date of the original patent.

Since no days in the periods of paragraphs (c)(1) and (c)(2) were on or before January 5, 1988, the number of days to be subtracted from the regulatory review period is zero.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) during which the Applicant did not act with due diligence.

In Applicant's opinion, marketing applicant acted with due diligence as defined at 35 U.S.C. §156(d)(3) during the above calculated periods of paragraphs (c)(1) and (c)(2). Accordingly, zero days are subtracted from the regulatory review period.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(I) and (ii) of this section (ignoring half days).

There are 1643 days in the period defined by paragraph (c)(1). Since there are no reductions in this time period pursuant to paragraphs (d)(1)(I) and (ii) of this section, the number of days remaining in the period defined by paragraph (c)(1) is 1643 days. One-half of 1643 days, ignoring half days for purposes of subtraction, is 821. Subtracting 821 days from 2812 results in a time period of 1991.

Thus, the period determined according to paragraph (d)(1) is 1991 days.

2. (d)(2) Date

The number of days determined in paragraph (d)(1), 1991 days, added to the original term of the patent, i.e., 20 years from the original filing date, results in an extended patent expiration date of February 18, 2015.

3. (d)(3) Date

Fourteen years added to the May 31, 1996, date of approval under the Federal Food, Drug and Cosmetic Act, yields an extended patent expiration date of May 31, 2010.

4. (d)(4) Date

Comparing the extended terms determined according to paragraphs (d)(2) and (d)(3), the earlier date is May 31, 2010.

5. (d)(5) Date

The original patent issued after September 24, 1984. Five years added to the original expiration date of the patent is September 6, 2014.

By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(I) of this section with each other, the earlier date is May 31, 2010.

6. (d)(6) Date

The original patent was issued after September 24, 1984. This section thus does not apply.

XIII. ACKNOWLEDGMENT OF DUTY TO DISCLOSE

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. §1.765.

XIV. APPLICATION FEE

Applicant submits herewith a check for $1060.00 in payment of the fee set forth at 37 C.F.R. §1.20(j).

The Commissioner is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to deposit Account No. 02-4800.

XV. CORRESPONDENCE ADDRESS

Please direct all correspondence and inquiries regarding this matter to:

Norman H. Stepno
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404
Phone: (703) 836-6620

XVI. DUPLICATE OF APPLICATION AND CERTIFICATION

Applicant encloses herewith a copy of the present application papers, and certifies that said copy is a duplicate of the application papers. For the convenience of the Senior Legal Advisor of the Patent Office, Applicant is also enclosing three (3) additional copies of the application.

XVII. DECLARATION

A Declaration pursuant to 37 C.F.R. §1.740(b) is attached hereto.

In view of the foregoing, an extension of the term of the above identified patent is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____

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Date: July 26, 1996

Patent
Attorney's Docket No. 010095-003g

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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U.S. Patent No.: 5,015,758	)	Attn: Box Patent Extension
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Issued: May 14, 1991	)	
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For: PROCESS FOR THE PREPARATION OF 1-ADAMANTANE DERIVATIVES	)	

DECLARATION UNDER 37 C.F.R. §1.740(a)(17)

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Donna M. Meuth, do hereby declare as follows:

I am a patent attorney or agent for the owner of record of the above identified U.S. Patent No. 5,015,758 for which a patent term extension is sought, authorized to practice before the U.S. Patent and Trademark Office, and have general authority from the owner to act on behalf of the owner in patent matters, including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. §1.740.

I have reviewed and understand the contents of the application being submitted herewith.

I believe that the patent is subject to extension pursuant to 37 C.F.R. §1.710.

I believe that an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations.

I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Donna M. Meuth
Registration No. 36,607

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Alexandria, Virginia 22313-1404
(703) 836-6620

Date: July 26, 1996

United States Patent [19]

Pilgrim et al.

[11] Patent Number: 5,015,758

[45] Date of Patent: May 14, 1991

[54] **PROCESS FOR THE PREPARATION OF 1-ADAMANTANE DERIVATIVES**

[75] Inventors: **William R. Pilgrim; Joel Lagiere, both of Valbonne, France**

[73] Assignee: **Centre International De Recherches Dermatologiques (CIRD), France**

[21] Appl. No.: **403,280**

[22] Filed: **Sep. 6, 1989**

[30] **Foreign Application Priority Data**

Sep. 7, 1988 [FR] France 88 11706

[51] Int. Cl.[5] C07C 69/76

[52] U.S. Cl. 560/56; 564/95; 568/62; 568/634; 568/732; 568/733; 568/737

[58] Field of Search 585/352; 560/56; 564/95; 568/62, 634, 732, 733, 737

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,883,603 5/1975 Inamoto et al. 560/56

4,087,410 5/1978 Dominianni et al. 568/766

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[57] **ABSTRACT**

A process for the preparation of 1-adamantane derivatives characterized by the fact that a 1-acyloxyadamantane, in which the acyl group contains 1 to 4 carbon atoms, is reacted with a receptor compound in a linear aliphatic or cycloaliphatic type solvent in the presence of concentrated sulfuric acid and at ambient temperature.

11 Claims, No Drawings

PROCESS FOR THE PREPARATION OF 1-ADAMANTANE DERIVATIVES

This invention provides a new process for the preparation of 1-adamantane derivatives.

The 1-adamantyl radical is present in a number of active compounds having therapeutic activity, particularly as a substituent for aromatic compounds. The known synthetic methods capable of producing these compounds employ a haloadamantane as the initial product, especially 1-chloroadamantane or 1-bromoadamantane.

The major drawback of these processes is that they release large quantities of hydrochloric or hydrobromic acid. It is, however, possible to eliminate such release by adding metallic sodium or a base having a high amine content to the reaction medium, but in this case byproducts are produced.

The use of 1-adamantanol trifluoroacetate in excess, without catalyst or solvent, has also been proposed, but this method of synthesis is not always reproducible and its use cannot be generally applied for other types of aromatic compounds.

In addition, similarly to the process which involves haloadamantanes, byproducts are formed, particularly those of the 1,3-disubstituted adamantane type.

The presence of these byproducts makes these methods of synthesis particularly difficult to implement on an industrial scale.

Indeed, one cannot consider their elimination by chromatography and so purification processes by recrystallization must be used, resulting in a considerable effect on the production costs.

Furthermore, these recrystallizations are not always capable of eliminating all of the byproducts.

The present invention offers a new process for the preparation of 1-adamantane derivatives, and especially a process for adamantylation of aromatic compounds, in which the reaction takes place at ambient temperature without the release of dangerous gases. In addition, this new process reduces the reaction times and has the major advantage of keeping the formation of byproducts to a minimum and even eliminating them entirely.

The new process according to this invention provides 1-adamantane derivatives in a very pure form at an excellent rate of yield, to the extent that their isolation on an industrial level can be achieved by addition of a hydroxylated organic solvent, followed by filtration and a possible washing with water.

Although the process of the present invention is highly recommended for the adamantylation of aromatic compounds, it can also be applied to the preparation of other compounds in the 1-adamantane series.

The object of this invention is a process for the preparation of 1-adamantane derivatives. This process consists in causing a reaction between a 1-acyloxy adamantane, the acyl radical of which contains from 1 to 4 carbon atoms, with a receptor compound, with the reaction taking place at ambient temperature in solution in a solvent of the linear aliphatic or cycloaliphatic type, in the presence of concentrated sulfuric acid.

According to the invention, the 1-acyloxyadamantane is preferably 1-formyloxyadamantane, 1-acetoxyadamantane, or 1-propionyloxyadamantane.

The linear aliphatic solvent is preferably hexane, heptane, or octane, and the cycloaliphatic solvent is preferably cyclopentane, cyclohexane, or cyclooctane

The proportion of solvent necessary to implement the process according to the invention is generally between 5 and 100 times the quantity of the 1-acyloxyadamantane used in the reaction and the proportion of concentrated sulfuric acid is generally between 0.1 and 0.5 part per part of 1-acyloxyadamantane.

According to a preferred method of implementation of the invention, the 1-acyloxyadamantane is prepared in situ by esterification of the 1-hydroxyadamantane or 1-adamantanol with an acid anhydride using concentrated sulfuric acid as the catalyst.

The carboxylic acid released during the esterification reaction does not have any adverse effect on the operation of the process of the invention.

The process according to the invention is more specifically intended for the adamantylation of aromatic compounds, and in this case the receptor compound can, for example, be anisole, phenol, toluene, naphthalene, thiophene, or furan and their substituted derivatives.

According to a preferred type of implementation, the aromatic receptor compound is:

4-bromoanisole
4-bromophenol
4-methoxybenzoic acid
methyl 4-methoxybenzoate
methyl 2-fluoro-4-methoxybenzoate
allyl 2-fluoro-4-hydroxybenzoate
methyl 6-(4-hydroxyphenyl)-2-naphthoate
methyl 6-(4-methoxyphenyl)-2-naphthoate
6-hydroxy-2-bromonaphthalene
6-methoxy-2-bromonaphthalene.

The receptor compound can also be a thiol, in which case the process according to this invention leads to the formation of an adamantyl thioether Among the thiols, special mention is made of 4-methoxybenzene thiol.

The receptor compound can also be a nitrile such as acetonitrile.

In this case the process according to the invention leads to the formation of an amide which can then be transformed under conventional conditions into 1-aminoadamantane (or 1-adamantanamine).

The following gives several non-limiting examples to illustrate the implementation of the process according to the invention.

EXAMPLE 1

Preparation of 2-(1-adamantyl)-4-bromo-1-methoxybenzene

(a) From 1-acetoxyadamantane

In a 100 ml three-necked flask are added, under nitrogen, 5 g of 1-acetoxyadamantane and 10 ml of n-heptane; after total solution, 1.26 g of concentrated sulfuric acid are added dropwise. At 20° C., 4.82 g of 4-bromoanisole are poured in and the mixture is agitated for 24 hours. Then, 60 ml of denatured ethanol are added and agitation is continued for 2 hours. The solid is filtered using sintered glass and then one dries in a vacuum oven at 20° C. for 24 hours; 5.67 g of expected raw product was collected. (Melting point: 144°-145° C.).

(b) From 1-adamantanol

In a ten-liter flask equipped with an agitation mechanism and a cooler are placed 750 g of 1-adamantanol and 2.4 l of n-heptane, under nitrogen. With good agitation, 18.3 g of concentrated sulfuric acid are slowly added and then 573.5 g of acetic anhydride. During the addition, the temperature rises from 21.C to approximately 37° C. Agitation is continued for 15 hours at approximately 21° C. and then 241.5 g of concentrated sulfuric acid are added. The temperature goes from 21° C. to 28° C. Once the temperature has returned to 21° C., 921.3 g of 4-bromoanisole are added and agitation is continued for 24 hours. 3 liters of denatured ethanol are added and one agitates for one hour. The solid product is collected by filtration and it is washed on the filter with 1 liter of absolute ethanol. After drying in a vacuum oven at 25° C. for 24 hours, one obtained 1.015 kg of desired raw product (Melting point: 142°–145° C.).

EXAMPLE 2

Preparation of 2-(1-adamantyl)-4-bromophenol

In a 100 ml three-necked flask, and under a nitrogen environment, is placed 1 g of 1-acetoxyadamantane and 10 ml of n-heptane. After total dissolution, 0.25 g of concentrated sulfuric acid is added drop by drop while keeping the temperature at 20° C., then 0.886 g of 4bromophenol is poured in slowly. After leaving 24 hours in vigorous agitation, 20 ml of denatured ethanol are added while maintaining the temperature at 20° C. Next, the solvent is evaporated to dryness under reduced pressure and a whitish raw product is obtained. The product is redissolved in water at approximately 60° C., it is washed to pH 6 and dried in a vacuum oven for 24 hours at 25° C. One collected 1.24 g of expected raw product (Melting point: 140°–141° C.).

EXAMPLE 3

Preparation of 3-(1-adamantyl)-4-methoxybenzoic acid

In a 100 ml three-necked flask, and under a nitrogen environment, are placed 1 g of 1-acetoxyadamantane and 50 ml of n-heptane. After dissolution, 0.25 g of concentrated sulfuric acid is added drop by drop at a temperature of approximately 22° C. and 0.783 g of 4-methoxybenzoic acid is poured in slowly. After leaving the mixture well agitated for 48 hours, 50 ml of denatured ethanol are added and the insoluble material is filtered Concentration of the filtrate volume to three quarters yields a solid white precipitate which is filtered with sintered glass. It is dried in a vacuum oven for 24 hours at 30° C. and 0.680 g of expected raw product was collected (Melting point: 245°–246° C.).

EXAMPLE 4

Preparation of methyl 3-(1-adamantyl)-4-methoxybenzoate

In a 100 ml three-necked flask, under a nitrogen environment, are placed 2 g of 1-acetoxyadamantane and 20 ml of n-heptane. After total dissolution, 0.5 g of concentrated sulfuric acid is added drop by drop. At a temperature of approximately 20.C, 1.71 g of methyl 4-methoxybenzoate is added slowly and agitated for 48 hours. The solid obtained is filtered with sintered glass and washed with water until neutrality is reached. After drying in a vacuum oven for 24 hours at 25 C, one recovered 2 g of expected raw product (Melting point: 136°–137° C.).

EXAMPLE 5

Preparation of methyl 5-(1-adamantyl)-2-fluoro-4methoxybenzoate

In a 100 ml flask, in a nitrogen atmosphere, are placed 2.48 g of I-adamantanol and 10 ml of n-heptane. Then 0.034 ml concentrated sulfuric acid and 1.76 ml of acetic anhydride are added dropwise. After one hour of agitation, there are added 0.87 ml of concentrated sulfuric acid and then a suspension of 2 g of methyl 2-fluoro-4-methoxybenzoate in 10 ml of cyclohexane. After 16 hours of reaction at room temperature, agitation is stopped and one separates the upper layer. The solvents heptane and cyclohexane are evaporated and then the product is extracted with dichloromethane. The organic phase is washed with aqueous bicarbonate solution, dried over magnesium sulfate and filtered on a Buchner funnel. After evaporation of the solvent under reduced pressure at 40° C., the product is dissolved in a 50:50 mixture of dichloromethane and hexane and then purified by filtration using a silica column. After passage of a liter of 50:50 dichloromethane/hexane eluent, one evaporates the solvents under reduced pressure at 30° C. and then dries the product in an oven at 50° C. for 24 hours. Thus were obtained 3 g of the pure product melting at 82°–88° C.

EXAMPLE 6

Preparation of allyl 3-(1-adamantyl)-2-fluoro-4hydroxybenzoate

In a 250 ml three-necked flask, under nitrogen, one introduces 3.04 g 1-adamantanol, 10 ml of n-heptane and 63 µl concentrated sulfuric acid. Dropwise, 2.16 ml of acetic anhydride are added and stirring is conducted for 3 hours at room temperature. Dropwise, 540 µl concentrated sulfuric acid are added and one adds portionwise 3.92 g of allyl 2-fluoro-4-hydroxybenzoate. After this addition, one adds 25 ml of dichloromethane and agitates at room temperature for 24 hours. After vacuum drying, the solid is taken up in water, neutralized to pH 7 with sodium bicarbonate and extracted with ethyl ether. The organic layer is washed with water and then with a concentrated aqueous sodium chloride solution. After drying over magnesium sulfate, one filters and evaporates the filtrate to obtain 7 g of crude product which is chromatographed on a silica column and eluted with dichloromethane. After trituration with hexane, filtration and drying in an oven at 50° C. there were obtained 3.86 g of the desired product, melting at 219°–222° C.

EXAMPLE 7

Preparation of methyl 6-[3-(1-adamantyl)-4-hydroxyphenyl-2-naphthoate

In a 100 ml three-necked flask, under a nitrogen environment, are placed 1 g of 1-acetoxyadamantane and 40 ml of n-heptane. After total solution, 0.25 g of concentrated sulfuric acid is added drop by drop. At 20° C., 1.43 g of methyl 6- (4-hydroxyphenyl)-2-naphthoate are poured in slowly and the mixture is left in vigorous agitation for 48 hours. After adding 40 ml of denatured ethanol and agitation for 2 hours, the solid is filtered and washed with heptane and then dried in a vacuum oven

for 24 hours at 30° C. One recovered 1.47 g of desired crude product (Melting point: 255°-256° C.).

EXAMPLE 8

Preparation of methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoate

In a 100 ml three-necked flask, are placed 1 g of 1-acetoxyadamantane and 50 ml of cyclohexane in a nitrogen environment. After total dissolution, 0.25 g of concentrated sulfuric acid is added drop by drop and 1 g of methyl 6-(4-methoxyphenyl)-2-naphthoate is added slowly. After leaving in vigorous agitation for 48 hours, 20 ml of denatured ethanol are added and the mixture is agitated for 2 hours. The solid obtained is filtered with sintered glass and washed abundantly with water until neutrality is reached. After drying at 30° C. for 24 hours in a vacuum oven, 1 g of desired raw product was obtained (Melting point: 221°-227° C.).

EXAMPLE 9

Preparation of 7-(1-adamantyl)-6-hydroxy-2-bromonaphthalene

In a 100 ml flask, under a nitrogen atmosphere, are placed 2 g of 1-acetoxyadamantane and 20 ml of n-heptane, and 0.5 g of concentrated sulfuric acid is introduced drop by drop. At a temperature of about 22.C, 2.3 of 6-hydroxy-2-bromonaphthalene are added slowly and the mixture is left in vigorous agitation. The solvent is eliminated by filtration and the solid residue in suspension in the water is collected. The residue is filtered and then washed until neutrality is obtained. The resulting reddish solid is washed again with hexane until a colorless filtrate is obtained. After drying in a vacuum oven for 24 hours at 30 C one obtains a raw product which is chromatographed with a silica column using an ethyl acetate and hexane mixture of 1:9 as the eluent. After evaporation of the solvents, 1.3 g of desired raw product were obtained (Melting point: 218°-224° C.).

EXAMPLE 10

Preparation of 7-(1-adamantyl)-6-methoxy-2-bromonaphthalene

In a 100 ml flask, under a nitrogen atmosphere, are placed 1 g of 1-acetoxyadamantane and 30 ml of n-heptane, and 0.25 g of concentrated sulfuric acid is introduced. At a temperature of about 20° C., 1.22 g of 2-bromo-6-methoxynaphthalene are poured in slowly and the mixture is left in vigorous agitation for 48 hours. Next, 20 ml of denatured ethanol are introduced and the mixture is evaporated to dryness under reduced pressure. The product is taken up in denatured ethanol and the precipitate is filtered with sintered glass. After drying of the raw product in a vacuum oven for 24 hours at 30° C., one purifies using silica column chromatography. There were obtained 0.4 g of the desired raw product (Melting point: 164°-168° C.).

EXAMPLE 11

Preparation of 2-(1-adamantyl)1-hydroxynaphthalene

A three-necked 100 ml flask is charged with 2.7 g of 1-acetoxyadamantane and 5 ml of cyclohexane in a nitrogen atmosphere. After complete dissolution, there are introduced 1.4 g of concentrated sulfuric acid. In a single portion there is added a suspension of 2 g of 1-naphthol in 15 ml of cyclohexane and one agitates for 45 minutes. 20 ml of ethanol are added and the mixture is filtered. One washes the residue with ethanol and with water and dries on the filter. After recrystallization with cyclohexane, one obtained 0.8 g of the desired product melting at 209.2°-209.6° C.

EXAMPLE 12

Preparation of (1-adamantyl)-4-methoxyphenyl sulfide

In a 100 ml three-necked flask, under a nitrogen environment, are placed 1 g of 1-acetoxyadamantane and 20 ml of n-heptane. After total dissolution, 0.25 of concentrated sulfuric acid is introduced dropwise. At a temperature of about 22.C, 0.63 ml of 4-methoxybenzenethiol is added using a syringe and it is left in vigorous agitation for 24 hours. Then, 20 ml of denatured ethanol are introduced and the mixture is concentrated under reduced pressure at 40° C. to obtain a raw product which is taken up in water. The product is then extracted using dichloromethane and the organic phase is washed with water until neutrality is reached. After evaporation of the organic phase, the residue is chromatographed using a silica column and a 1:4 mixture of dichloromethane and hexane as the eluent. After evaporation of the solvents, one obtains 1 g of desired raw product (Melting point: 70°-72° C.).

EXAMPLE 13

Preparation of 1-adamantyl-n-acetamide

Under a nitrogen atmosphere a 50 ml flask is charged with 1 g of 1-acetoxyadamantane and 10 ml of n-heptane. After complete solution, there are added dropwise 0.2 ml of concentrated sulfuric acid. At approximately 20° C., one adds dropwise 0.27 ml of acetonitrile and agitates for 24 hours. After filtration with a sintered glass filter, one recovers a white solid which is then placed in suspension in 20 ml of demineralized water. After agitation for 1 hour at room temperature, the product is filtered and dried in an oven at 60° C. for 24 hours. There were thus obtained 450 mg of desired product melting at 148°-150° C.

We claim:

1. A process for the preparation of 1-adamantane derivatives characterized by the fact that a 1-acyloxyadamantane, in which the acyl group contains 1 to 4 carbon atoms, is reacted with a receptor compound in a linear aliphatic or cycloaliphatic type solvent in the presence of concentrated sulfuric acid and at ambient temperature.

2. A process according to claim 1 wherein the 1-acyloxyadamantane is 1-formyloxyadamantane, 1-acetoxyadamantane, or 1-propionyloxyadamantane.

3. A process according to claim 1 wherein the linear aliphatic solvent is hexane, heptane, or octane.

4. A process according to claim 3 wherein the solvent is heptane.

5. A process according to claim 1 wherein the cycloaliphatic solvent is cyclopentane, cyclohexane, or cyclooctane.

6. A process according to claim 1 wherein the solvent is used in a proportion of between 5 and 100 times the quantity of the 1-acyloxyadamantane.

7. A process according to claim 1 wherein the concentrated sulfuric acid is used in a proportion of between 0.1:1 and 0.5:1 in relation to the quantity of 1-acyloxyadamantane.

8. A process according to claim 1 wherein the receptor compound is an aromatic compound of the group

consisting of anisole, phenol, toluene, naphthalene, thiophene, or furan and their substituted derivatives.

9. A process according to claim 7 wherein the receptor is

4-bromoanisole
4-bromophenol
4-methoxybenzoic acid
4-methoxybenzoate
methyl 2-fluoro-4-methoxybenzoate
allyl 2-fluoro-4-hydroxybenzoate
methyl 6-(4-hydroxyphenyl)-2-naphthoate
methyl 6-(4-methoxyphenyl)-2-naphthoate or
6-hydroxy-2-bromonaphthalene.

10. A process according to claim 1 wherein the receptor compound is 4-methoxybenzene thiol.

11. A process according to claim 1 wherein the receptor compound is acetonitrile.

* * * * *

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1	5,015,758	183	960	----	07/403,280	05/14/91	09/06/89	04	NO	PAID

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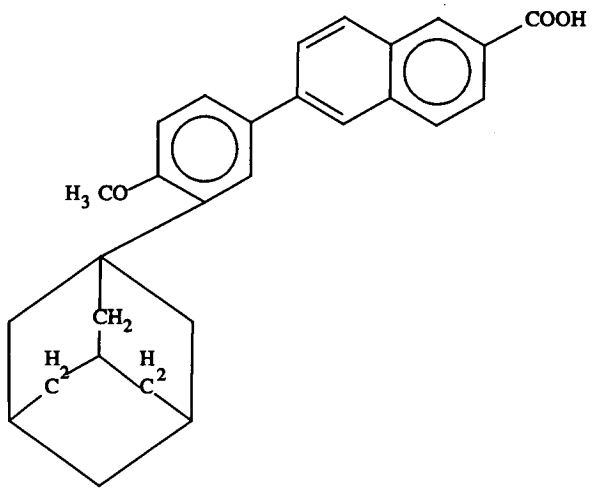
APPENDIX C



Adapalene